CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074894

Trade Name : DILTIAZEM HYDROCHLORISE INJECTION 5MG/ML

Generic Name: Diltiazem Hydrochloride Injection 5mg/ml

Sponsor : Gensia Laboratories, Ltd.

Approval Date: August 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074894

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Chemistry Review(s)	X			
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Pharmacology Review(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074894

APPROVAL LETTER

ANDA 74-894

AUG 26 1997

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

Dear Sir:

This is in reference to your abbreviated new drug application dated April 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Injection, 5 mg/mL.

Reference is also made to your amendments dated January 10, July 1, July 7, and August 13, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diltiazem Hydrochloride Injection, 5 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cardizem® Injection, 5 mg/mL, of Hoechst Marion Roussel Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

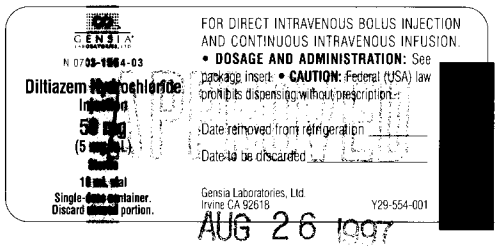
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074894

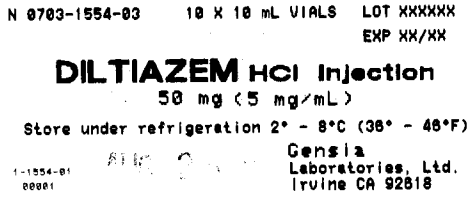
FINAL PRINTED LABELING

10 mL Container Label
(Part No. Y29-554-001)



10 mL Tray (Carton) Label
(Part No. Y29-554-201)

10 mL Shelf Pack "B" Label
(Part No 1-1554-01)



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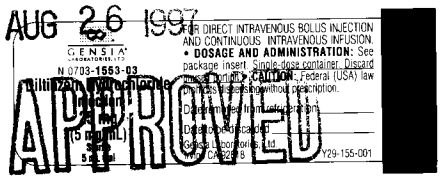

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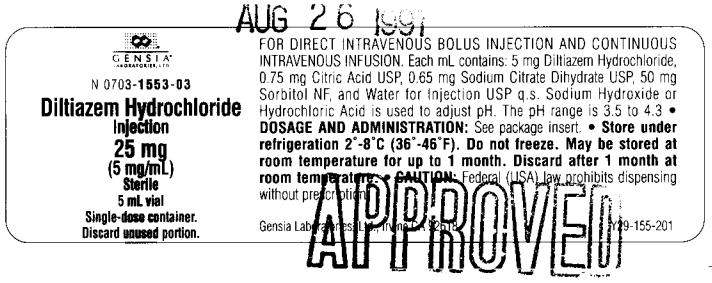
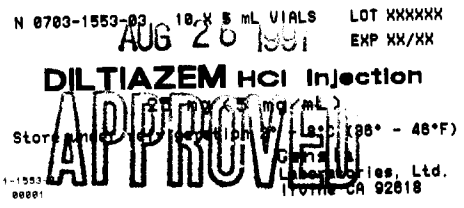
(Part No. Y29-155-201)



5 mL Shelf Pack "B" Label
(Part No 1-1553-01)



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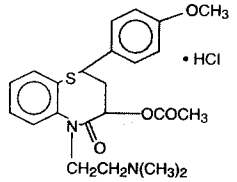
LABORATORIES, LTD.

Diltiazem Hydrochloride Injection

DESCRIPTION

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel antagonist). Chemically, diltiazem hydrochloride is (+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate(ester) monohydrochloride. The structural formula is:



$C_{22}H_{26}N_2O_4S \cdot HCl$

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.99.

Diltiazem Hydrochloride Injection is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.5 to 4.3.

Diltiazem Hydrochloride Injection is for direct intravenous bolus injection and continuous intravenous infusion.

Each mL contains: 5 mg Diltiazem Hydrochloride, 0.75 mg Citric Acid USP, 0.65 mg Sodium Citrate Dihydrate USP, 50 mg Sorbitol NF, and Water for Injection USP q.s. Sodium Hydroxide or Hydrochloric Acid is used to adjust pH. The pH range is 3.5 to 4.3.

CLINICAL PHARMACOLOGY

Mechanisms of Action

Diltiazem inhibits the influx of calcium (Ca^{2+}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of diltiazem in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. Diltiazem exhibits frequency (use) dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

Diltiazem slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. Diltiazem converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, e.g., Wolff-Parkinson-White syndrome (WPW).

Diltiazem prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction. Diltiazem has no significant electrophysiologic effects on tissues in the heart that are fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways.

Like other calcium channel antagonists, because of its effect on vascular smooth muscle, diltiazem decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

Hemodynamics

In patients with cardiovascular disease, diltiazem administered intravenously in single bolus doses, followed in some cases by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary vascular resistance and increased coronary blood flow. In a limited number of studies of patients with compromised myocardium (severe congestive heart failure, acute myocardial infarction, hypertrophic cardiomyopathy), administration of intavenous diltiazem produced no significant effect on contractility, left ventricular and diastolic pressure, or pulmonary capillary wedge pressure. The mean ejection fraction and cardiac output/index remained unchanged or increased. Maximal hemodynamic effects usually occurred within 2 to 5 minutes of an injection. However, in rare instances, worsening of congestive heart failure has been reported in patients with preexisting impaired ventricular function.

Pharmacodynamics

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers using the Sigmoidal E_{max} model. Changes in heart rate, systolic blood pressure, and diastolic blood pressure did not correlate with diltiazem plasma concentrations in normal volunteers. Reduction in mean arterial pressure correlated linearly with diltiazem plasma concentration in a group of hypertensive patients.

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in HR and plasma diltiazem concentration using the Sigmoidal E_{max} model. Based on this relationship, the mean plasma diltiazem concentration required to produce a 20% decrease in heart rate was determined to be 80 ng/mL. Mean plasma diltiazem concentrations of 130 ng/mL and 300 ng/mL were determined to produce reductions in heart rate of 30% and 40%.

Pharmacokinetics and Metabolism

Following a single intravenous injection in healthy male volunteers, diltiazem appears to obey linear pharmacokinetics over a dose range of 10.5 to 21.0 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of diltiazem is approximately 305 L. Diltiazem is extensively metabolized in the liver with a systemic clearance of approximately 65 L/h.

After constant rate intravenous infusion to healthy male volunteers, diltiazem exhibits nonlinear pharmacokinetics over an infusion range of 4.8 to 13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64 to 48 L/h while the plasma elimination half-life increases from 4.1 to 4.9 hours. The apparent volume of distribution remains unchanged (360 to 391 L). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered bolus doses ranging from 2.5 mg to 38.5 mg, systemic clearance averaged 36 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Based on the results of pharmacokinetic studies in healthy volunteers administered different ***oral*** diltiazem formulations, constant rate intravenous infusions of diltiazem at 3, 5, 7, and 11 mg/h are predicted to produce steady-state plasma diltiazem concentrations equivalent to 120-, 180-, 240-, and 360-mg total daily oral doses of diltiazem hydrochloride tablets or diltiazem hydrochloride extended-release capsules.

After oral administration diltiazem undergoes extensive metabolism in man by deacetylation, N-demethylation, and O-demethylation via cytochrome P-450 (oxidative metabolism) in addition to conjugation. Metabolites N-monodesmethyldiltiazem, desacetyldiltiazem, desacetyl-N-monodesmethyldiltiazem, desacetyl-O-desmethyldiltiazem, and desacetyl-N, O-desmethyldiltiazem have been identified in human urine. Following oral administration, 2% to 4% of the unchanged diltiazem appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Following single intravenous injection of diltiazem, however, plasma concentrations of N-mono-desmethyldiltiazem and desacetyldiltiazem, two principal metabolities found in plasma after oral administration, are typically not detected. These metabolites are observed, however, following 24 hour constant rate intravenous infusion. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours of diltiazem.

Diltiazem is 70% to 80% bound to plasma proteins. *In vitro* studies suggest $alpha_1$-acid glycoprotein binds approximately 40% of the drug at clinically significant concentrations. Albumin appears to bind approximately 30% of the drug, while other constitutents bind the remaining bound fraction. Competitive *in vitro* ligand binding studies have shown that diltiazem binding is not altered by therapeutic concentrations of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenylbutazone, propranolol, salicyclic acid, tolbutaminde, or warfarin.

Renal insufficiency, or even end-stage renal disease, does not appear to influence diltiazem disposition following ***oral*** administration. Liver cirrhosis was shown to reduce diltiazem's apparent ***oral*** clearance and prolong its half-life.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Injection is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of Diltiazem Hydrochloride Injection.

The use of Diltiazem Hydrochloride Injection for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of Diltiazem Hydrochloride Injection was effective in reducing heart rate by at least 20% in 95% of patients. Diltiazem Hydrochloride Injection rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of Diltiazem Hydrochloride Injection, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of Diltiazem Hydrochloride Injection in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be

Y36-114-301
Package Insert

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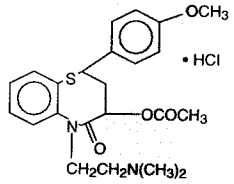

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similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following Diltiazem Hydrochloride Injection.

In domestic controlled trials, bolus administration of Diltiazem Hydrochloride Injection was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of Diltiazem Hydrochloride Injection.

CONTRAINDICATIONS

Diltiazem Hydrochloride Injection is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (e.g., verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with Diltiazem Hydrochloride Injection. As such, the initial use of Diltiazem Hydrochloride Injection should be, if possible, in a setting when monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of superventricular origin from that of ventricular origin prior to administration of Diltiazem Hydrochloride Injection.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see PRECAUTIONS, Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of Diltiazem Hydrochloride Injection in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with Diltiazem Hydrochloride Injection therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphate, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with Diltiazem Hydrochloride Injection. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted to significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to potential for additive effects, caution is warranted in patients receiving Diltiazem Hydrochloride Injection concomitantly with other agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. Dilitiazem undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug—drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of Diltiazem Hydrochloride Injection with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis. Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs after AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers. Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility of bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving the renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued.

The effect of cyclosprine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of ***oral*** diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine (by 40 to 72%), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of Diltiazem Hydrochloride Injection in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1300 patients were similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (e.g., itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Asystole, atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.

Dermatologic: Pruritus, sweating.

Gastrointestinal: Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.

Nervous System: Dizziness, paresthesia.

Other: Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with Diltiazem Hydrochloride Injection, the following events associated with oral diltiazem may occur.

Cardiovascular: AV block (third degree), bundle branch block, ECG abnormality, palpitations, syncope, tachycardia, ventricular extrasystoles.

Dermatologic: Alopecia, erythema multiforme, (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, leukocytoclastic vasculitis, petechiae, photosensitivity, purpura, rash, urticaria.

Gastrointestinal: Anorexia, diarrhea, dysgeusie, dyspepsia, mild elevations of SGPT and LDH, thirst, weight increase.

Nervous System: Abnormal dreams, amnesia, depression, extrapyramidal symptoms, gait abnormality, hallucinations, insomnia, nervousness, personality change, somnolence, tremor.

Other: Allergic reactions, angioedema (including facial or periorbital edema), CPK elevation, epistaxis, eye irritation, gingival hyperplasia, hemolytic anemia, hyperglycemia, impotence, increased bleeding time, leukopenia, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, retinopathy, sexual difficulties, thrombocytopenia, tinnitus.

Events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease for the patient.

OVERDOSAGE

Overdosage experience is limited. In the event of overdosage or an exaggerated response, appropriate supportive measures should be employed. The following measures should be considered:

Bradycardia: Administer atropine (0.6 to 1.0 mg). If there is no response to vagal blockade administer isoproterenol cautiously.

High-degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose.

The intravenous LD_{50}'s in mice and rats were 60 and 38 mg/kg, respectively. The toxic dose in man is not known.

DOSAGE AND ADMINISTRATION

Direct Intravenous Single Injections (Bolus)

The initial dose of Diltiazem Hydrochloride Injection should be 0.25 mg/kg actual body weight as a bolus administered over 2 minutes (20 mg is a reasonable dose for the average patient). If response is inadequate, a second dose may be administered after 15 minutes. The second bolus dose of Diltiazem Hydrochloride Injection should be 0.35 mg/kg actual body weight administered over 2 minutes (25 mg is a reasonable dose for the average patient). Subsequent intravenous bolus doses should be individualized for each patient. Patients with low body weights should be dosed on a mg/kg basis. Some patients may respond to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Experience with this dose is limited.

Continuous Intravenous Infusion

For continued reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an intravenous infusion of Diltiazem Hydrochloride Injection may be administered. Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) Diltiazem Hydrochloride Injection and reduction of heart rate, begin an intravenous infusion of Diltiazem Hydrochloride Injection. The recommended initial infusion rate of Diltiazem Hydrochloride Injection is 10 mg/h. Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.

Diltiazem shows dose-dependent, non-linear pharmacokinetics. Duration of infusion longer than 24 hours and infusion rates greater than 15 mg/h have not been studied. Therefore, infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/h are not recommended.

Dilution

To prepare Diltiazem Hydrochloride Injection for continuous intravenous infusion aseptically transfer the appropriate quantity (see chart) of Diltiazem Hydrochloride Injection to

Diluent Volume	Quantity of Diltiazem Hydrochloride Injection to Add	Final Concentration	Administration	
			Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1.0 mg/mL	10 mg/h 15 mg/h	10 mL/h 15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h 15 mg/h	12 mL/h 18 mL/h
500 mL	250 mg (50 mL) Final Volume 500 mL	0.45 mg/mL	10 mg/h 15 mg/h	22 mL/h 33 mL/h

*5 mg/h may be appropriate for some patients.

the desired volume of either Normal Saline, D5W, or D4W/0.45% NaCl. Mix thoroughly. Use within 24 hours. Keep refrigerated until use.

Diltiazem Hydrochloride Injection was tested for compatibility with three commonly used intravenous fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. Diltiazem Hydrochloride Injection was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinylchloride (PVC) bags at controlled room temperature 15-30°C (59-86°F) or under

refrigeration 2-8°C (36-46°F).

- dextrose (5%) injection USP.
- sodium chloride (0.9%) injection USP.
- dextrose (5%) and sodium chloride (0.45%) injection USP.

Because of potential physical incompatiabilities, it is recommended that Diltiazem Hydrochloride Injection not be mixed with any other drugs in the same container.

If possible, it is recommended that Diltiazem Hydrochloride Injection not be co-infused in the same intravenous line.

Physical incompatibilities (precipitate formation or cloudiness) were observed when Diltiazem Hydrochloride Injection was infused in the same intravenous line with the following drugs; acetazolamide, acyclovir, aminophylline, ampicilin, ampicilin sodium/sulbactam sodium, cefamandole, cefoperazone, diazepam, furosemide, hydrocortisone sodium succinate, insulin, (regular: 100 units/mL), methylprednisolone sodium succinate, mezlocillin, nafcillin, phenytoin, rifampin, and sodium bicarbonate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Transition to Further Antiarrhythmic Therapy

Transition to other antiarrhythmic agents following administration of Diltiazem Hydrochloride Injection is generally safe. However, reference should be made to the respective agent manufacturer's package insert for information relative to dosage and administration.

In controlled clinical trials, therapy with antiarrhythmic agents to maintain reduced heart rate in atrial fibrillation or atrial flutter or for prophylaxis of PSVT was generally started within 3 hours after bolus administration of Diltiazem Hydrochloride Injection. These antiarrhythmic agents were intravenous or oral digoxin, Class 1 antiarrthythmics (e.g., quinidine, procainamide), calcium channel blockers, and oral beta-blockers.

Experience in the use of antiarrhythmic agents following maintenance infusion of Diltiazem Hydrochloride Injection is limited. Patients should be dosed on an individual basis and reference should be made to the respective manufacturer's package insert for information relative to dosage and administration.

HOW SUPPLIED

Diltiazem Hydrochloride Injection 5 mg/mL is supplied as follows:

NDC Number		
0703-**1553-03**	25 mg	5 mL vial
0703-**1554-03**	50 mg	10 mL vial

Packaged 10 vials per shelfpack.

SINGLE-DOSE CONTAINERS. DISCARD UNUSED PORTION.

Store Diltiazem Hydrochloride Injection under refrigeration 2°-8°C (36°-46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Issued: July 1997

Gensia Laboratories, Ltd.
Irvine CA 92618

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074894

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-894

3. NAME AND ADDRESS OF APPLICANT
Gensia Laboratories, Ltd.
19 Hughes
Irvine, CA 92718

4. LEGAL BASIS FOR SUBMISSION
Cardizem® Injection
Hoechst Marion Roussel Inc.
P.O. Box 8480
Kansas City, MO 64114

There are no outstanding patents or exclusivities.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Diltiazem HCl Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
4/30/96 Original Submission.
1/10/97 Amendment - Response to Agency's letter of 12/2/96.
3/5/97 Correspondence - Clarification of address for drug substance manufacturer.

FDA:
5/14/96 Receipt Acknowledged.
8/19/96 Issuance of Bioequivalence No Further Questions letter.
12/2/96 Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

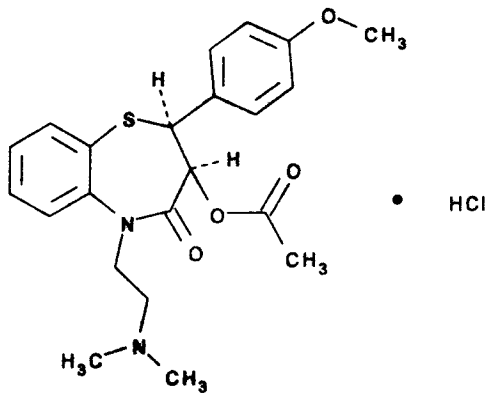
13. DOSAGE FORM
Injection
5 mL and 10 mL vials

14. POTENCY
5 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

$C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.99



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation +98.3 ± 1.4° (c = 1.002 in methanol), 110° - 116° in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

7/10/96 - Microbiology review #1, J. McVey.
8/1/96 - Labeling review, C. Hoppes.
8/12/96 - Bioequivalence waiver, K. Dhariwal.
11/18/96 - Chemistry review #1, G.J. Smith.

17. COMMENTS

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found satisfactory.

A waiver of in vivo bioequivalence requirements was granted by the Division of Bioequivalence.

An acceptable EIR was issued by the Office of Compliance.

An acceptable Methods Validation report (with recommended modifications) was issued by the District Laboratory. Firm has committed to resolve issues with Laboratory.

The DMF for drug substance was found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: July 10, 1997.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074894

BIOEQUIVALENCE REVIEW(S)

ANDA 74-894

Gensia Laboratories, Inc.
Attention: Donald J. Harringan, R.Ph.
19 Hughes
Irvine CA 92718-1902

AUG 19 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Injection 5 mg/mL, 5 mL and 10 mL vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 12 1996

Diltiazem Hydrochloride Injection
5 mg/mL; 5 mL and 10 mL vials
ANDA #74-894
Reviewer: Kuldeep R. Dhariwal
File name: 74894W.496

Gensia Laboratories
19 Hughes
Irvine, CA 92718
Submission Date:
April 30, 1996

Review of a Waiver Request

Introduction:

Diltiazem hydrochloride injection is indicated for atrial fibrillation and paroxysmal supraventricular tachycardia. It is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7-4.1. Diltiazem hydrochloride is a white to off-white crystalline powder, soluble in water. The reference listed drug is Cardizem® injectable 5 mg/mL available in 5 and 10 mL single dose vials and is manufactured by Marion Merrell Dow. This is not a first generic application.

Background:

The firm requests a waiver for evidence of bioavailability for its test product diltiazem hydrochloride injection, 5 mg/mL in accordance with 21 CFR 320.22 (b)(1).

Formulation:

Ingredients	Test mg/mL	Reference mg/mL
Diltiazem Hydrochloride, USP	5.00	5.00
Citric acid, anhydrous	0.75	0.75
Sodium Citrate, Dihydrate	0.65	0.65
Sorbitol, NF	50.0	-
Sorbitol Solution, USP	-	71.4*
Sodium Hydroxide	Adjust pH	Adjust pH
Hydrochloric acid	Adjust pH	Adjust pH
Water for injection, USP	q.s. to 1 mL	q.s. to 1 mL

* equivalent to 50 mg of sorbitol

Comments:

1. The route of administration, dosage form, and amount of active ingredient are same in test and reference drug products.

2. The firm states (page 42) that inactive ingredients differ only in that test formulation utilizes sorbitol, instead of sorbitol solution, 70% USP. The total concentration of sorbitol is identical in test and reference products.

3. The firm formulates its diltiazem hydrochloride injection to a pH range of 3.6-3.8 (release specification [redacted]). The labeling states a pH range of 3.5 to 4.3. This pH range corresponds to their shelf specification which is based on the diltiazem hydrochloride injection monograph published in the Pharmacopeial Forum volume 20, number 5 (September/October, 1994). Diltiazem hydrochloride injection monograph is not in USP 23. Marion Merrell Dow's labeling for Cardizem® Injectable specifies a pH range of 3.7-4.1. The Division of Chemistry should evaluate the firm's pH specification of 3.5-4.3.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories demonstrates that diltiazem hydrochloride injection 5 mg/mL falls under 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product diltiazem hydrochloride injection 5 mg/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Cardizem® Injectable manufactured by Marion Merrell Dow.

[redacted] /S/ 3/8/96

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence